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EFFECTS OF DAILY OR WEEKLY THERMAL (FOOTPAD) STRESS UPON MANIFESTATION OF MELANOMA TUMOURS[1]

GILLIAN DUGGAN, OKSANA PEREDERY, AND M. A. PERSINGER

Laurentian University

Summary.—A total of 48 C57 male and female mice received thermal stimulation to their footpads either daily, weekly, or never. After either two or three weeks of this treatment the mice were injected to discern if the initiation of carcinogenic cell proliferation during a stressful period would influence the rate of development of the tumour. The latency in days for the onset of a discernable node over the injection site was measured. A statistically significant interaction between the temporal pattern of treatments and sex explained about 25% of the variance in the latency of the appearance of tumours. *Post hoc* analysis showed the source of interaction involved the group that had not received the thermal stress. The results may suggest that either weekly or daily thermal stress may have reduced the females' resistance to tumorigenesis. However, this pattern and type of stress did not influence the first appearance of these skin tumours in the males.

The temporal pattern of stimuli can influence the rate of cell division of aberrant cells within the body. For example, Sklar and Anisman (1979) found that a single nociceptive event (foot shock) facilitated tumour growth more than repeated nociceptive events. The present study was designed to discern if daily or weekly exposures to thermal nociception would affect the latency of the appearance of melanoma tumours, a form of skin cancer involving the abnormal growth of pigment-producing melanocytes. The selection of these two interstimulus intervals was based upon the response of the rodent's cellular immunity to single stressors (Missaghi, Richards, & Persinger, 1992). We expected that the acute (daily) treatment would suppress the immune system and facilitate the growth of the mass of the tumour.

A total of 48 male ($n=24$) and female ($n=24$) C57 mice, 120 days of age at the beginning of the study, were subjects. Four mice of the same sex were maintained per cage. Water and food were available *ad libitum*. Room temperature was controlled within 1° of 20° C.

Equal numbers of male and female mice were randomly assigned to one of three treatments: control, weekly stress, or daily stress. Mice from the last group were placed once per day for 3 wk. on a commercial hotplate designed to measure thermal nociceptive thresholds; the temperature was set at 56° C. The second group received the treatment once per week for 3 wk. The criterion for removal from the plate was licking of the hind paws twice or after 60 sec. had elapsed to minimize potential tissue damage to the footpads. The third group remained within the home cage and were called the nontreated group.

At the beginning of either the second or third week of treatment, all mice were injected (100 µl) in the right rear flank with 1 million syngeneic melanoma cells. The mice were examined by careful touch every other day for 27 days (maximum score) for the discernable onset of a tumour. All mice were killed, and the conspicuous black gelatinous mass that defines the

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body of the tumour was confirmed by visual inspection. Samples were verified histologically at 400X and 1000X with toluidine blue O stain. The aberrant, irregularly shaped cells that define this cell line's morphology were obvious. The onset days were analyzed by three-way analysis of variance (treatment, time of inoculation, sex) by SPSS software.

The analysis showed a statistically significant interaction ($F_{1,36}=3.42$, $p<.05$; ω^2 estimate = 24% of variance explained) between treatment and sex. *Post hoc* Tukey ($p<.05$) analysis indicated the primary source of the interaction was the difference between the male and female mice in the nontreated groups. The means and standard deviations in days after the inoculation for the onset of a palpable node in the injection site for the males in the nontreated, weekly thermal stress, and daily thermal stress groups were 14.0 ($SD=5.1$), 12.4 ($SD=6.3$), and 15.9 ($SD=5.2$), respectively. These values for the females were 22.6 ($SD=6.2$), 15.3 ($SD=7.2$), and 14.8 ($SD=2.4$), respectively. The statistically significant main effect for sex ($F_{1,36}=5.25$, $p<.05$; eta = .28) was confounded by the interaction. There were no other statistically significant differences.

These results did not strongly confirm the reports of Sklar and Anisman (1979). However, their stressor (electric shock) and tumour source were different than the ones employed in the present study. The expected earlier onset of tumours for mice that received the acute treatment was not statistically significant. It is possible the effects of the present type of daily or weekly stress were not discernible because daily handling of all mice to detect the presence of tumours may have reduced the discrepancy between the stressed and "nonstressed" mice.

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